FORMULATION AND EVALUATION OF FLUCONAZOLE SOLID DISPERSION INCORPORATED GEL USING POLYMERS AS CONTROLLED RELEASE DOSAGE FORMS: DEVELOPMENT, CHARACTERIZATION AND IN VITRO EVALUATION.

DR. C.S. CHAUHAN*1, DHARMENDRA SINGH SISODIYA¹

ABSTRACT

Introduction: Fluconazole an antifungal agent applied topically for its action against the fungal infection in the form of semisolid formulation. solid dispersion incorporated gel of fluconazole for topical delivery system using gelling agent as HPMC, Polyvinyl pyrrolidone, polyethylene glycol 6000,

Purpose: The aim of this study was to formulate and evaluation of solid dispersion incorporated gel for better percutaneous absorption and provide stability. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability.

Methods: fluconazole solid dispersion prepared by physical mixture, solvent evaporation method and fusion method using carrier such as PVP, PEG6000 and urea. The higher solubility and release showed in solvent evaporation method. The gelling agent HPMC selected as gel formulation.

Evalution: Formulation was evaluated for pH, viscosity and in vitro diffusion study.

Results: The result that solid dispersion incorporated gel showed higher permeability and diffusion.

Conclusion: The best-fit release kinetics was achieved with Koresmeyer-Peppas plot followed by zero order and First order. The release of fluconazole was influenced by the drug to polymer ratio and particle size & was found to be both diffusion and dissolution controlled.

KEY WORDS

Fluconazole, gel, solid dispersion, Solvent Evaporation technique, polymer, control drug delivery system.

AFFILIATION

Address for Correspondence:

B.N. COLLEGE OF PHARMACY, UDAIPUR.
INTRODUCTION

Fluconazole, a synthetic triazole derivative, is an azole antifungal agent. Fluconazole is an antifungal agent applied topically for its action against the fungal infection in the form of semisolid formulation. It is commonly marketed under the trade name Diflucan® or Trican. The necessity of physical characterization of drug and its suitability for particular type of formulation is must for its development. Fluconazole is indicated in the prophylaxis and treatment of esophageal, oropharyngeal, disseminated, chronic mucocutaneous, and vulvovaginal candidiasis; coccidioidomycosis; cryptococcal meningitis; onychomycosis; febrile neutropenia; fungal pneumonia; fungal septicemia; tinea corporis, tinea cruris, tinea pedis, and tinea manuum. Fluconazole is FDA approved for the treatment of systemic candidal infections and is an appropriate, less toxic alternative to amphotericin B.

Fluconazole is fungistatic and may be fungicidal, depending on the concentration. Azole antifungals interfere with fungal cytochrome P450 enzyme activity necessary for the demethylation of 14-alpha-methyl sterols to ergosterol, the principal sterol in fungal cell membranes. As ergosterol is depleted, the fungal cell membrane is damaged. Unlike ketoconazole, fluconazole has a very weak, noncompetitive inhibitory effect on the liver cytochrome P450 enzyme system, while maintaining a high affinity for fungal cytochrome P450 enzyme activity. In Candida albicans, azole antifungals inhibit transformation of blastospores into invasive mycelial form. Fluconazole has not been reported to have antiandrogenic activity at currently used doses, and does not affect cortisol metabolism in patients treated with clinically recommended doses.

Solid dispersion is an effective technique which can easily enhance the dissolution rate of drugs. Subcutaneous absorption of Fluconazol with solid dispersion was significantly greater than that obtained with an intact drug. The present study was performed to investigate the dissolution behavior and topical absorption characteristics of Fluconazol from solid dispersion incorporated gels, tend to avoid typical side effect of antifungal associated with oral and systemic administration. To improve the permeability of Fluconazol, the use of gel bases is a logical approach to increase the drug flux across the epithelium. To determine the diffusion properties of drugs in semisolid vehicles especially when the release of drug is at the application site is likely to be rate limited by the diffusion of the drug. The ability of vehicle to release the drug at the local site is limited by numerous factors such as drug-vehicle, drug-skin and vehicle-skin interaction. In this paper the influence of Fluconazol solid dispersion on diffusion from HPMC gel base was investigated in order to develop the effective semisolid formulation of Fluconazol.

MATERIALS AND METHODS

Chemicals

Fluconazole, Polyvinyl pyrrolidone, polyethylene glycol 6000, HPMC was purchased from Loba Chem Pvt. Ltd (Mumbai). Urea, mannitol, sodium hydroxide were purchased from S.D. Fine chemical Pvt. Ltd, (Mumbai) All the chemicals used in the present study were of AR Grade.
Preparation of solid dispersions

Preparation of physical mixture\(^6\)

The physical mixture of Fluconazol prepared using PEG6000, PVP & urea in 1:1, 1:2 and 1:3 ratios were obtained by mixing pulverized powders of drugs and various carriers with the help of a spatula.

Preparation by solvent evaporation method\(^7,8\)

The required amount of Fluconazol and carrier in 1:1, 1:2 & 1:3 ratio were dissolved in sufficient volume of methanol with continuous stirring. The solvent from the solution was removed at 45° with continuous stirring to obtain dry mass. The dried mass was pulverized passed through 44 mesh sieve and stored in desiccator until used for further studies.

Preparation by fusion method\(^8\)

Solid dispersion of Fluconazol & carriers in ratios of 1:1, 1:2 & 1:3 were obtained by melting carrier in a porcelain dish at 80 – 85° and to this Fluconazol added with thorough mixing for 1-2 minutes followed by quick cooling. The dried mass was the pulverized passed through 44 mesh sieve and stored in a desiccator until used for further studies.

Characterization of solid dispersions

The prepared solid dispersion were evaluated for drug carrier interaction using differential scanning calorimetric (DSC – Pyris – 6) and FTIR (Perkin Elmer 1600 series) spectral studies. For DSC studies samples were sealed in aluminum pans and the DSC

Thermo grams were recorded at a heating rate of 10°/min from 100°C – 300°C. FTIR spectrum was carried by KBR pellet method. The solid dispersions were also characterized for appearance. The displacement value of solid dispersions and pure drug was determined.

In vitro dissolution studies for solid dispersions\(^9\)

The USP dissolution apparatus (Type-II) was used for evaluation of in vitro release profile of solid dispersions. The dissolution medium was 900ml phosphate buffer of pH 7.4 kept at 37 ± 0.1°. The drug or physical mixture or solid dispersion was filled in capsule and then kept in the basket of dissolution apparatus, which was then rotated at 50 rpm. Samples of 5ml were with drawn at specified time intervals and analyzed spectrophotometrically at 275 nm. Withdrawn samples were replaced by fresh buffer solution.

Preparation of solid dispersion incorporated gels\(^10\)

HPMC Gel:

Weighed quantity of HPMC soaked in 75ml water for 24 hours then glycerin, DMSO was added with stirring. The solid dispersions containing 1% drug was dissolved in ethanol and this dry solution was added to above gel with continuous stirring.
Physical characterization of Gels

Physical characterization such as spreadability, extrudability, viscosity, PH, drug content was measured.

**Determination of spreadibility**

The spreadibility of the formulations was determined by an apparatus suggested by Mutimer et al, which was suitable modified in the laboratory and used for the study. It consists of a wooden block which was provided by a pulley at one end. A rectangular ground glass plate was fixed on the block. An excess of gels (about 2 g) under study was placed on this ground plate. The gel was then sandwiched between this plate and another glass plate having the dimensions of the ground plate and provided with the hook. A 300gm weight was placed on the top of two plates for five minutes to expel air and the provide a uniform film of the gel between the plates. Excess of gel was scrapped off from the edges. The top plate was then subjected to a pull of 30g. with the help of a string attached to the hook and the time (in sec) required by the top plate to cover a distance of 10cms was noted. The spreadibility was calculated using the formula. \[ S = \frac{m}{l/t} \]

where, \( S \) = spreadibility, \( m \) = weight tied to the upper glass slide, \( l \) = length of the glass side and \( t \) = time taken in seconds.

**Determination of Extrudability**

The apparatus used for extrudability was suitably fabricated in the laboratory. It consist of a wooden block inclined at an angle of 45° fitted with a thin, long metal strip (tin) at one end. While the other end was free. The aluminium tube containing 10gm of gel was positioned on inclined surface of wooden block 30gm weight was placed on free end of the aluminium strip and just touched for 10 seconds. The quantity of gel extruded from each tube was noted.

**Determination of viscosity**

Viscosity of prepared gels was determined by Brook field programmable DV-II viscometer.

**Determination of pH**

pH of formulation determined by dispersing 0.5 gm of gel in 50 ml of water. It was checked using digital pH meter at constant temperature. Prior to this, the pH meter was calibrated using buffer solution of pH 4.0 and 9.2, and then electrode was washed with demineralised water. The electrode was then directly dipped in to gel formulation and constant reading as noted.

**Determination of drug content**

One gm of solid dispersion incorporated gel was mixed with methanol, diluted to 100ml then after filtering the stock solution, filtrate was diluted suitably and absorbance was measured against blank at 275nm.
In vitro diffusion studies for solid dispersion incorporated gels

The in-vitro diffusion studies for the gels were carried out by apparatus consist of cylindrical glass tube which was opened at both the ends 1gm of gel formulation equivalent to 10gm of Fluconazol was spread uniformly on the surface of cellophane membrane (previously soaked in water for overnight). Whole assembly was fixed in such a way that the lower end of tube containing gel was just touched the surface of diffusion medium i.e. 100ml PH 7.4 phosphate buffer contained in 150ml beaker which was placed in water bath and maintained at 37 ± 2°C, the contents were stirred using magnetic stirrer at 5 ± 5 rpm. The sampling was done at different time intervals over a period of 6 hours and absorbance was measured at 275 nm using shimadzu UV-visible spectrophotometer.

Table 1: Formulation of Fluconazole dispersion.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Drug carrier ratio</th>
<th>Method</th>
<th>Carrier</th>
<th>Formulation code</th>
<th>Drug carrier ratio</th>
<th>Method</th>
<th>Carrier</th>
<th>Formulation code</th>
<th>Drug carrier ratio</th>
<th>Method</th>
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<tbody>
<tr>
<td>GP1</td>
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<td></td>
<td>Mannitol</td>
<td>MF1</td>
<td>1:1</td>
<td></td>
<td>PVP</td>
<td>VS1</td>
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<td></td>
<td></td>
<td>MF2</td>
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<td></td>
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<td>VS3</td>
<td>VS3</td>
<td>1:3</td>
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<td>VP1</td>
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<td></td>
<td>PEG6000</td>
<td>GF1</td>
<td>1:1</td>
<td>Fusion</td>
<td>PEG6000</td>
<td>GS1</td>
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<td>VP2</td>
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<td>Physical mixture</td>
<td>GF2</td>
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<td></td>
<td>GS2</td>
<td>GS2</td>
<td>1:2</td>
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<td></td>
<td>GF3</td>
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<td>Urea</td>
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<td></td>
<td>UF3</td>
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Table 2: Formulation of Fluconazole solid dispersion.

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<tr>
<th>Ingredients</th>
<th>HGP3</th>
<th>HGF3</th>
<th>HGS3</th>
<th>HVP3</th>
<th>HUF3</th>
<th>HVS3</th>
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<tr>
<td>SD equivalent to 1gm of Fluconazole</td>
<td>4.0</td>
<td>4.0</td>
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<tr>
<td>HPMC (gm)</td>
<td>4.0</td>
<td>5.0</td>
<td>6.0</td>
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<td>Ethanol (ml)</td>
<td>8.0</td>
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<tr>
<td>DMSO (ml)</td>
<td>0.25</td>
<td>0.25</td>
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<tr>
<td>Glycerol (ml)</td>
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<td>5.0</td>
<td>5.0</td>
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<tr>
<td>Dist water (ml)</td>
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<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
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Table 3: Physical characteristics of Fluconazole solid dispersion incorporated gels.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>PH</th>
<th>Drug content (%)</th>
<th>Viscosity (Cp)</th>
<th>Spreadibility (gcm/s)</th>
<th>Extrudability</th>
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<td>HGF3</td>
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<td>96.33</td>
<td>384</td>
<td>11.42</td>
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<tr>
<td>HGS3</td>
<td>7.0</td>
<td>95.56</td>
<td>832</td>
<td>8.58</td>
<td>+</td>
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<tr>
<td>HVP3</td>
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<td>98.16</td>
<td>292</td>
<td>16.79</td>
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<td>HUF3</td>
<td>6.6</td>
<td>98.89</td>
<td>384</td>
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<tr>
<td>HVS3</td>
<td>6.8</td>
<td>97.04</td>
<td>832</td>
<td>8.61</td>
<td>+</td>
</tr>
</tbody>
</table>

+  → Satisfactory  ++  → Good

Fig 1: Percent release of Fluconazole from (GP1, GP2 & GP3), (VP1, VP2 & VP3) & (UP1, UP2 & UP3) prepared by physical mixing.
Fig.2: Percent release of Fluconazole from (MF1, MF2 & MF3), (GF1, GF 2 & GF 3) & (UF1, UF 2 & UF 3) prepared by fusion method
RESULTS AND DISCUSSION

Dissolution profile

The in vitro release studies of different batches of solid dispersions are shown in figure 1, 2 and 3. The solid dispersion prepared by solvent evaporation showed improved dissolution when compared with physical mixtures, fusion method and pure drug. Among the solid dispersions prepared 1:3 ratio showed greater solubility than the others. Because of enhanced/ greater release solid dispersion prepared with 1:3 drug carrier ratios was selected as ideal batch for incorporation into gels. Physical characteristics of Fluconazole solid dispersion incorporated gels: Physical characteristics were measured according to the methods describe above.

The results and listen in Table 3. The in vitro diffusion studies were performed by over a period of 6 hours and results are shown in figure 4. The dissolution rate of Fluconazol from solid dispersion is significantly higher than that of pure drug. Solid dispersion prepared by fusion method showed faster drug release than prepared by. Solvent evaporation followed by physical mixture. IR studies indicated that no chemical interaction between drug and carrier took place during preparation of solid dispersion of Fluconazole.
CONCLUSION

The in vitro diffusion study of Fluconazole solid dispersion incorporated gels was greatly improved when compared with those of intact Fluconazol incorporated gels. From overall formulations HVP3 was found to be the best formulations. From the above results, it may be concluded that solid dispersion incorporated gels were better for improvement of dissolution and diffusion of Fluconazole and also to overcome gastric side effect of the drug.

REFERENCES

1. AHFS Drug Information - 2003; p. 90
2. USP DI - 2003; p. 304-305
